Cholesterol lowering and mortality: the importance of considering initial level of risk

George Davey Smith, Fujian Song, Trevor A Sheldon

Abstract

***Objective*—To investigate the level of risk of death from coronary heart disease above which cholesterol lowering treatment produces net benefits.**

***Design*—Meta-analysis of results of randomised controlled trials of cholesterol lowering treatments.**

***Methods*—Published and unpublished data from all identified randomised controlled trials of cholesterol lowering treatments with six months or more follow up and with at least one death were included in the meta-analysis. The analyses were stratified by the rate of death from coronary heart disease in the control arms of the trials.**

***Main outcome measures*—Death from all causes, from coronary heart disease, and from causes other than coronary heart disease.**

***Results*—In the pooled analysis, net benefit in terms of total mortality from cholesterol lowering was seen only for trials including patients at very high initial risk of coronary heart disease (odds ratio 0·74; 95% confidence interval 0·60 to 0·92). In a medium risk group no net effect was seen, and in the low risk group there were adverse treatment effects (1·22; 1·06 to 1·42). In a weighted regression analysis a significant ($p < 0·001$) trend of increasing benefit with increasing initial risk of coronary heart disease was shown. Raised mortality from causes other than coronary heart disease was seen in trials of drug treatment (1·21; 1·05 to 1·39) but not in the trials of non-drug treatments (1·02; 0·88 to 1·19). Cumulative meta-analysis showed that these results seem to have been stable as new trials appeared.**

***Conclusion*—Currently evaluated cholesterol lowering drugs seem to produce mortality benefits in only a small proportion of patients at very high risk of death from coronary heart disease. Population cholestrol screening could waste resources and even result in net harm in substantial groups of patients. Overall risk of coronary heart disease should be the main focus of clinical guidelines, and a cautious approach to the use of cholesterol lowering drugs should be advocated. Future trials should aim to clarify the level of risk above which treatment is of net benefit.**

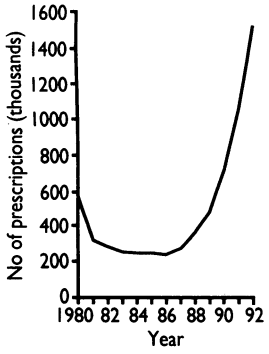

FIG 1—*Prescriptions for cholesterol lowering drugs, England, Wales, and Scotland, 1980 to 1992. Source: Department of Health; NHS Scotland Common Services Agency; Welsh Health Common Services Agency*

Department of Public Health, University of Glasgow, Glasgow G12 8RZ
George Davey Smith, *senior lecturer in epidemiology and public health*

Nuffield Institute for Health, University of Leeds, Leeds LS2 9JT
Fujian Song, *research fellow*

Centre for Health Economics, University of York, York YO1 5DD
Trevor A Sheldon, *senior research fellow in medical statistics*

Correspondence to:
Dr Davey Smith.

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Introduction

Prescriptions for cholesterol lowering drugs increased more than sixfold between 1986 and 1992 in Great Britain (fig 1). The increasing volume of prescriptions for these agents is even more impressive elsewhere in the world, with lipid lowering agents currently being one of the most dynamic growth areas for pharmaceutical sales.[1] At the same time there is vigorous debate regarding the appropriate domain for pharmaceutical cholesterol lowering.[2] Although the epidemiological evidence linking raised concentrations of circulating cholesterol with risk of coronary heart disease is robust[3] and concerns that naturally low cholesterol levels could lead to increased mortality from other causes may well be unfounded,[4] the overall impact of therapeutic cholesterol lowering on mortality has been brought into question. Various meta-analyses of randomised controlled trials of cholesterol lowering have generally shown a reduction in risk of coronary heart disease,[5-14] but there has been a tendency for mortality from other causes to be increased, leading to therapeutic cholesterol lowering having no overall effect on total mortality. The reported lack of impact on total mortality has been rationalised as being due to the relatively small size of the existant studies, rendering them of low power to examine this outcome.[15] Contrary to one of the objectives of the technique of meta-analysis, rather than reducing uncertainty such overviews of cholesterol lowering trials have fuelled scepticism and debate, with controversy often focusing on which trials should be included in the analyses. However, establishing the current best evidence is necessary, given that treatment decisions regarding individual patients continue to need to be made and public health policy determined.[16]

The reductions in risk of coronary heart disease brought about through cholesterol lowering would be expected to translate into benefits in terms of overall mortality most readily among individuals at a particularly high risk of death from coronary heart disease. In line with this expectation the mortality outcome of cholesterol lowering treatment seems to be more favourable in trials recruiting patients with pre-existing cardiovascular disease (secondary prevention) than in trials largely involving participants without such disease (primary prevention).[13 17]

This division into primary and secondary prevention studies, however, does not directly reflect a stratification according to risk of death from coronary heart disease, since investigators have used different criteria regarding what constitutes a primary or secondary prevention trial. Thus, while some of the secondary prevention studies have recruited patients soon after a definite myocardial infarction[1a 8a]—a group with a very high risk of death from coronary heart disease—other such studies have enrolled participants on the basis of any evidence of existing coronary disease,[27a 34a] generally a group at lower risk of death from coronary heart disease. Similarly, while some of the primary prevention studies have included detailed examinations to exclude subjects with coronary disease,[28a 29a] other primary prevention studies have included a known or unknown proportion of participants who demonstrably had[16a 20a 30a] or are likely to have had[33a] evidence of existing coronary disease. Trials used in the meta-analysis are listed separately in the references.]

As the groups of participants included in the randomised trials of therapeutic cholesterol lowering were highly heterogeneous, with a 100-fold range in mortality from coronary heart disease (see table I), the

potential benefits of cholesterol lowering would be expected to vary widely between studies, rendering the results of meta-analyses, which are pooled estimates of efficacy, difficult to interpret. The present analysis, which includes important new trial data that have recently been published[1a 19b 27a 31b] or that we have obtained (see acknowledgments), examines the manner in which the outcome of cholesterol lowering is related to initial risk of coronary heart disease and the implications of this for current practice with regard to pharmacological treatments to lower cholesterol concentrations.

Methods

Using Medline and BIDS (Bath Information Data Services), previous overviews, and information from experts, we identified all randomised controlled single factor trials of cholesterol lowering treatment with at least six months of follow up in which at least one death occurred. For one study[18] it proved impossible to ascertain in which arm of the trial the solitary death occurred, leaving 35 trials[1a-35a] for inclusion in this meta-analysis.

Published data have been supplemented through contacts with the researchers (see acknowledgments). We also identified several trials of cholesterol lowering of six months or longer in which it was not clear whether any deaths occurred. Contact with the authors established that there were no deaths during the trials in all but two of these studies, for which this was impossible to establish clearly.[19 20] Details of all trials, and the data included in the meta-analysis, are available on request (see acknowledgments).

Pooled treatment effects were estimated by calculating a weighted average of odds ratios of deaths in the treatment and control groups of studies using the random effects method.[21] This method, used because of heterogeneity between individual study estimates, weights each study by the inverse of the marginal variance of each treatment difference. This marginal variance is the sum of the individual study sampling error and an estimate of the between study variance. Thus larger studies with more fatal events have more influence on the pooled estimate. The random effects model generally produces wider confidence intervals for the pooled estimate than fixed effects methods,[22] it is therefore more conservative with regard to the range of likely treatment effects.

The trials are summarised in table I. They are ranked by the death rate from coronary heart disease per 1000 person years that was observed in the control group of each study. This indexes the degree of risk of death from coronary heart disease that existed for the participants enrolled in the studies, a level of risk that is revealed by the mortality from coronary heart disease of those subjects who were randomly allocated to receive no treatment. It was calculated by dividing the number of deaths from coronary heart disease occurring in the control group by an approximation of the person years at risk in the study, then presented per 1000 person years, using the formula:

$$\left(\frac{\text{Coronary heart disease death}}{\text{years of follow up} \times (\text{number alive at end of trial} + 0{\cdot}5\,(\text{number dying during study}))}\right) \times 1000$$

Recently Brand and Kragt have argued that the pooled odds ratio can be misleading as a summary of evidence from a number of trials if there is a simple and clinically relevant risk indicator by which the trials can be ordered in the analysis.[23] Previous meta-analyses have separated trials into primary and secondary prevention studies, generally using a classification assigned by the trialists,[7 9 11 13 24] but as table I shows there is considerable overlap in the risk of death from coronary heart disease between these two categories of study. Therefore our meta-analysis has been stratified by risk of death from coronary heart disease in the control group. Further, weighted linear regressions of the log of the odds ratio for mortality have been fitted, against the mortality from coronary heart disease per 1000 person years in the control arm of the trials (risk of coronary heart disease) as the explanatory variable, to examine the strength of the association between level of risk of coronary heart disease and treatment effects.

Since most of the controversy surrounding previous

TABLE I—*Randomised clinical trials on effects of cholesterol lowering treatment on coronary heart disease (CHD) included in meta-analysis*

Reference No designation (year of publication)	CHD deaths per 1000 person years in control groups	Predominant patient group	Treatment/control	Follow up (years)	Subjects* Sex (age)	Subjects* No (treatment/control)	Baseline serum cholesterol (mmol/l)	Total mortality (odds ratio (95% confidence interval))
1a Singh (1992)	127·5	Secondary	Strict diet/diet	2	MF (NA)	204/202	5·9	0·47 (0·27 to 0·81)
2a Marmorston (1962)	110·4	Secondary	Oestrogen/placebo	5	M (50-70)	285/147	NA	0·93 (0·59 to 1·48)
3a Stamler (1963)	78·8	Secondary	Oestrogen/placebo	5	M (<50)	156/119	6·4	0·61 (0·36 to 1·04)
4a McCaughan (1981)	72·7	Secondary	Probucol/placebo	1	M (50)	88/30	7·9	0·21 (0·02 to 1·96)
5a Harrold (1969)	63·5	Diabetes	Clofibrate/placebo	1	MF (NA)	30/33	NA	0·00 (0·00 to 2·62)
6a Stockholm (1988)	62·1	Secondary	Clofibrate-niacine/usual	5	MF (59-63)	279/276	6·4	0·66 (0·45 to 0·97)
7a Oslo Diet (1970)	56·0	Secondary	Diet/usual	5	M (30-64)	206/206	7·7	0·68 (0·43 to 1·08)
8a Low Fat (1965)	50·9	Secondary	Low fat diet/usual	3	M (<65)	123/129	6·8	0·85 (0·42 to 1·71)
9a DART (1989)	50·5	Secondary	Low fat diet/no low fat diet	2	M (<70)	1018/1015	6·5	0·98 (0·74 to 1·29)
10a VA drug (1968)	50·3	Secondary	Various drugs/placebo	3·2	M (28-75)	427/143	6·2	1·01 (0·62 to 1·63)
11a Newcastle (1971)	48·9	Secondary	Clofibrate/placebo	5	MF (<65)	244/253	6·5	0·58 (0·34 to 0·96)
12a Oliver (1961)	43·7	Secondary	Oestrogen/lactose	5	M (35-64)	50/50	6·1	1·63 (0·63 to 4·32)
13a Acheson (1972)	39·5	Secondary	Clofibrate/placebo	6	MF (NA)	47/48	7·5	1·34 (0·55 to 3·27)
14a STARS (1992)	36·4	Secondary	Cholestyramine/diet/usual	3	M (<66)	30/60	7·2	0·00 (0·00 to 3·01)
15a,b CDP (1975)	35·6	Secondary	Various drugs/placebo	8	M (30-64)	5552/2789	6·5	1·01 (0·91 to 1·12)
16a-c Dayton (1969)	32·4	Primary	Diet/usual	<8	M (>55)	424/422	6·1	0·95 (0·73 to 1·25)
17a Soya Bean (1968)	29·1	Secondary	Soya bean oil/usual	2-6·7	M (<60)	199/194	7·0	0·86 (0·48 to 1·55)
18a,b Scottish (1971)	27·3	Secondary	Clofibrate/placebo	6	MF (40-69)	350/367	7·0	0·91 (0·57 to 1·44)
19a,b Sahni (1991)	26·5	Secondary	Lovastatin/usual	2	MF (60)	79/78	5·4	0·78 (0·15 to 3·78)
20a Upjohn (1978)	21·7	Primary	Colestipol/placebo	1-3	MF (51/57)	1149/1129	7·9	0·75 (0·47 to 1·18)
21a Sydney (1978)	21·5	Secondary	Diet/usual	2-7	M (30-59)	221/237	7·3	1·60 (0·92 to 2·79)
22a Rose (1965)	20·8	Secondary	Olive and corn oil/usual	2	MF (<70)	54/26	6·7	4·35 (0·52 to 200·50)
23a NHLIB (1984)	17·5	Secondary	Cholestyramine/placebo	5	NA	71/72	8·4	0·70 (0·17 to 2·73)
24a Minnesota (1989)	11·5	Primary	Diet/usual	1	MF (NA)	4541/4516	5·4	1·08 (0·90 to 1·30)
25a POSCH (1990)	10·9	Secondary	Partial ileal surgery/control	9·7	MF (30-64)	421/417	6·5	0·75 (0·49 to 1·15)
26a CLAS (1987)	5·7	Secondary	Colestipol-niacine/placebo	2	M (40-59)	94/94	6·3	0·00 (0·00 to 39·00)
27a Frick (1993)	5·1	Secondary	Gemfibrozil/placebo	5	M (49)	311/317	6·9	1·65 (0·75 to 3·69)
28a LCCPPT (1984)	3·2	Primary	Cholestyramine/placebo	7·4	M (35-59)	1906/1900	7·2	0·95 (0·68 to 1·34)
29a Frick (1987)	1·9	Primary	Gemfibrozil/placebo	5	M (40-55)	2051/2030	6·9	1·06 (0·68 to 1·66)
30a-c EXCEL (1991)	1·3	Primary	Lovastatin/placebo	0·9	MF (18-70)	6582/1663	6·7	2·79 (0·82 to 11·40)
31a,b WHO (1978)	1·2	Primary	Clofibrate/olive oil	5·3	M (30-59)	5331/5296	6·8	1·31 (1·07 to 1·60)
32a Ornish (1990)	0·0	Secondary	Diet/usual	1	MF (35-75)	28/20	6·1	
33a SCOR (1990)	0·0	Familial hypercholesterolaemia	Various drugs plus diet/diet	2	MF (19-72)	48/49	9·6	0·33 (0·00 to 39·81)
34a FATS (1990)	0·0	Secondary	Various drugs plus diet/diet	2·5	M (<62)	94/52	7·0	
35a Gross (1973)	0·0	Secondary	Colestipol/placebo	1	MF (55/58)	23/29	8·0	0·61 (0·01 to 12·64)

*M=male; F=female; age=range of age or average age of subjects; NA=not available.

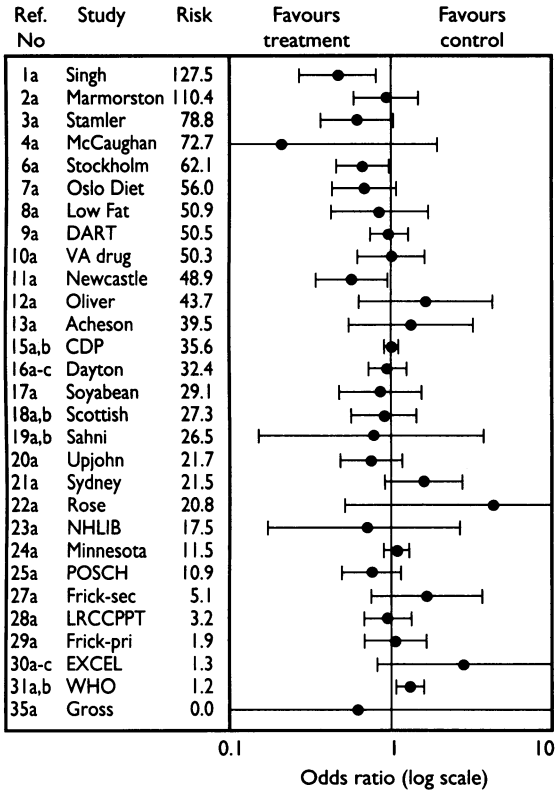

FIG 2—*Effect of treatment in relation to risk of death from coronary heart disease (defined by number of deaths from coronary heart disease per 1000 person years in control subjects). Six studies with no deaths in either group were excluded*

overviews and the principal motivation behind calls for larger randomised controlled trials has centred on the question of net changes in total mortality, this was used as the primary end point in this analysis.

Results

The estimated benefit, in terms of total mortality, in trials ordered according to revealed risk of coronary heart disease, as indicated by mortality due to coronary heart disease per 1000 person years in the control arms, is presented in figure 2. There is a definite trend in the odds ratios, with increasing net mortality benefit being seen with increasing risk of coronary heart disease. The weighted linear regression of the log of the odds ratio for total mortality against risk of coronary heart disease (CHD-risk; the mortality from coronary heart disease per 1000 person years in the control arm of the trials) as the independent variable gave the following regression equation:

$$\log_e(\text{odds ratio}) = 0{\cdot}184 - 0{\cdot}0061\ \text{CHD-risk} \quad (0{\cdot}0015)$$

This shows a statistically significant linear relation between the estimate of treatment effect—the log of the odds ratio for total mortality—and risk of coronary heart disease ($p < 0{\cdot}001$). Therefore the higher the mortality from coronary heart disease, the greater the net benefit of cholesterol lowering. This equation indicates that positive net benefit, in terms of reduction in total mortality, can be expected in groups where the mortality from coronary heart disease in untreated subjects is over 3·0% a year (fig 3). When the mortality from coronary heart disease in untreated subjects is below this level the analysis suggests that there is increased total mortality in the treatment groups.

The odds ratios for total mortality, mortality from coronary heart disease, and mortality from other causes are also shown stratified by the level of "revealed risk" (table II, fig 4). This analysis shows that although there seem to be benefits associated with lowering cholesterol for high risk groups, this is not true in intermediate and lower risk groups. The magnitude of the benefit (or disbenefit) in terms of deaths avoided (or induced) per 1000 person years will depend on both the odds ratio and the underlying death rate. In the high risk trials, the odds ratio of 0·74 translates into an improvement in mortality of 16·5/1000 person years, while in the low risk trials the odds ratio of 1·22 translates into a deterioration in mortality of 1·2/1000 person years.

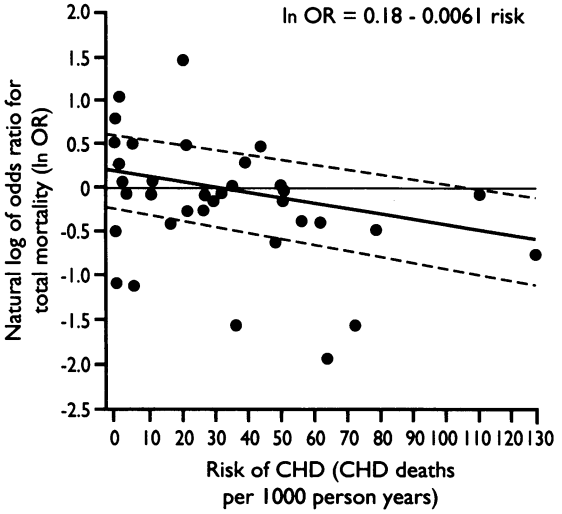

FIG 3—*Effect of treatment in relation to risk of death from coronary heart disease (CHD)*

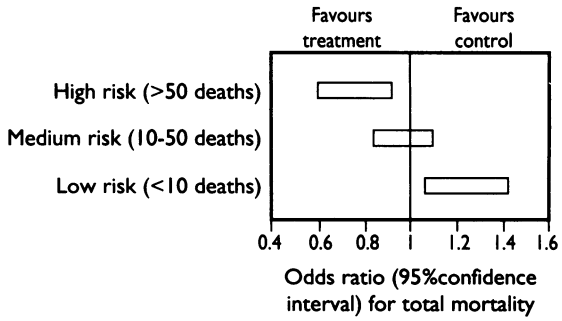

FIG 4—*Effect of cholesterol lowering treatment on total mortality stratified by number of deaths from coronary heart disease per 1000 person years in control subjects*

The use of the coronary heart disease death rate in the control group as the basis for stratification may be considered to introduce some bias, since high rates of deaths from coronary heart disease occurring by chance in the control arm of a trial would tend to reduce the odds ratio, overestimating the effect of treatment in reducing mortality (and vice versa). The large range of coronary heart disease death rates observed in the trials included in the meta-analysis, however, makes it unlikely that this will be a major source of bias. In addition, repeating the regression analysis using the mortality from coronary heart disease averaged over both the treatment and control groups yielded similar results: the coefficient in the regression

TABLE II—*Effects of cholesterol lowering, studies stratified by risk of death from coronary heart disease (CHD)*

No of CHD deaths per 1000 person years	No of trials	No of subjects	Odds ratio (95% confidence interval)		
			Death from CHD	Death from other causes	Total death
High risk group (>50/1000 person years)	10	5 116	0·74 (0·60 to 0·91)	0·95 (0·65 to 1·40)	0·74 (0·60 to 0·92)
Medium risk group (10-50/1000 person years)	15	24 090	0·92 (0·77 to 1·09)	1·07 (0·94 to 1·21)	0·96 (0·84 to 1·09)
Low risk group (<10/1000 person years)	10	27 918	1·15 (0·80 to 1·64)	1·33 (1·09 to 1·63)	1·22 (1·06 to 1·42)

Pooled odds ratio is calculated by using random effect method.

model was −0·0060 (p=0·001) in this case, rather than −0·0061 when control group mortality from coronary heart disease alone was used. With regard to treatment choices for patients, it is their risk of coronary heart disease if they remain untreated that can usefully contribute to treatment decisions, which is why this has been used as the principal stratification variable.

The sensitivity of the efficacy of cholesterol lowering according to risk of death from coronary heart disease reflects reductions in coronary heart disease mortality and increases in mortality from other causes. In groups with lower risk of coronary heart disease the benefits of cholesterol lowering were outweighed by apparent negative effects of interventions. Table III shows the effects of cholesterol lowering separately for drug and non-drug treatments, stratified above and below a coronary heart disease death rate of 30/1000 person years in the control group, the level above which overall net benefit of treatment was indicated by the regression analysis (fig 3). This confirms that the benefit of cholesterol lowering is confined to high risk groups and that the raised mortality from other causes seen in table II was evident only in drug interventions. That this adverse effect is a feature of drug treatment only is supported by the statistical significance (p=0·025) attached to the non-drug/drug dummy variable introduced into the regression analysis.

One possible factor confounding the association between treatment effect and initial risk of death from coronary heart disease is the reduction in cholesterol levels achieved by the interventions. To examine this we performed a weighted linear regression of the log odds ratio of mortality against percentage reduction in cholesterol in the treatment group and risk of coronary heart disease. Data on cholesterol reduction were not available for two of the trials. The coefficient for risk of coronary heart disease at −0·0087 (p<0·001), became somewhat more negative with the addition of percentage reduction in cholesterol concentration to the model. The odds ratio for the treatment effect on death from coronary heart disease in the trials was also significantly related to the percentage reduction in cholesterol concentration (coefficient −0·027; p=0·01) with risk of coronary heart disease in the model, suggesting that greater degrees of cholesterol lowering result in greater reductions in coronary heart disease death rates in the treated groups. Conversely, deaths from other causes were not statistically significantly related to reduction in cholesterol level; if anything, mortality from other causes was lower when cholesterol reduction was greater (−0·020; p=0·07), confirming that cholesterol reduction in itself is unlikely to produce increased risk of death from non-coronary causes.

Recently, cumulative meta-analysis, in which a meta-analysis is performed each time a new trial appears, has been advocated for tracking the results of trials and observing when an estimate of treatment effect stabilises around a central value.[25] The cumulative analysis for total mortality according to strata of risk of death from coronary heart disease (fig 5) shows that the different estimates of treatment effect reported in figure 3 and table II are relatively stable over time and are not the result of the particular moment at which we conducted this analysis.

TABLE III—*Effects of cholesterol lowering in trials using drug and non-drug intervention, studies stratified by risk of death from coronary heart disease (CHD)*

Trials stratified by risk of death from CHD	No of trials	No of subjects	Odds ratio (95% confidence interval)		
			Death from CHD	Death from other causes	Total deaths
Drug trials:					
Higher risk group*	11	11 106	0·78 (0·60 to 1·02)	1·14 (0·92 to 1·41)	0·81 (0·64 to 1·04)
Lower risk group†	13	31 165	0·97 (0·75 to 1·27)	1·27 (1·05 to 1·53)	1·08 (0·90 to 1·28)
All drug trials	24	42 271	0·87 (0·73 to 1·03)	1·21 (1·05 to 1·39)	0·94 (0·81 to 1·08)
Non-drug trials:					
Higher risk group*	6	4 009	0·79 (0·63 to 0·98)	0·98 (0·76 to 1·26)	0·80 (0·63 to 1·01)
Lower risk group†	6	10 874	1·09 (0·80 to 1·49)	1·05 (0·87 to 1·27)	1·07 (0·82 to 1·40)
All non-drug trials	12	14 883	0·90 (0·74 to 1·10)	1·02 (0·88 to 1·19)	0·90 (0·76 to 1·09)

One study (STARS[14]) has a drug and a diet arm and is reported here as two separate trials.
* ≥ 30 Deaths from CHD per 1000 person years.
† < 30 Deaths from CHD per 1000 person years.

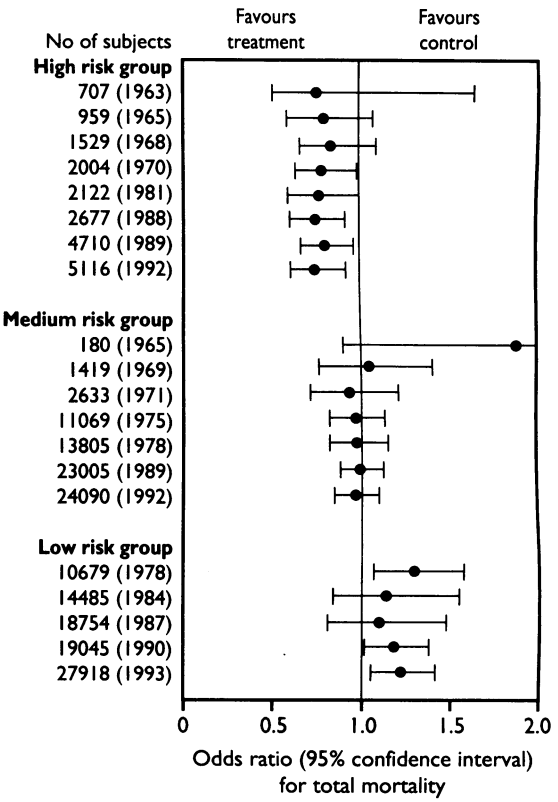

FIG 5—*Cumulative meta-analysis of effect of cholesterol lowering treatment on total mortality stratified by risk (number of deaths from coronary heart disease per 1000 person years in control subjects: high risk >50, medium risk 10-50, low risk <10)*

Discussion

Appropriate clinical practice and public health policy with regard to cholesterol lowering must be firmly based on actual demonstration of benefit. The meta-analysis reported here shows that the magnitude —and even existence—of such net benefits depends strongly on the level of risk of coronary heart disease

There is reasonable evidence that therapeutic cholesterol lowering produces greater benefits in terms of reduction in the incidence of non-fatal coronary heart disease events than in deaths from coronary heart disease.[26] The trials available for our analysis, however, did not consistently obtain reliable data regarding such non-fatal events. Possible bias due to the unblinded assessment of morbidity due to coronary heart disease, together with the fact that data on morbidity from other conditions were generally not collected,[27] make such end points unsuitable for use in meta-analyses aimed at establishing overall treatment benefit. Total mortality is clearly the end point least subject to potential bias.

Most cholesterol lowering interventions can influence coronary heart disease and overall mortality risk through mechanisms other than the cholesterol lowering itself. Examples include the fact that partial ileal bypass results in weight loss, blood pressure reduction, and improved glucose tolerance, in addition to cholesterol lowering[25a]; that the diets which produced cholesterol lowering in some of the trials have also influenced blood pressure and haemostatic mechanisms[1a]; that clofibrate lowers the coronary heart disease risk factor fibrinogen[28]; and that aspirin was given to patients receiving niacin but not to the control group in some trials.[26a] These additional effects would

all tend to lead to overestimation of the benefit of cholesterol lowering, since they would be expected to reduce the risk of coronary heart disease in the treatment arm over and above that consequent on cholesterol lowering itself. Despite this, such trials have been included in the present—and in previous—meta-analyses. On the other hand, some previous overviews have excluded certain trials on the grounds that the treatments used to lower cholesterol seem to have had adverse effects independent of the cholesterol lowering.[14 29] Such asymmetrical handling of this issue clearly introduces the possibility that the selection criteria for the studies to be included in the meta-analysis become data derived. The appropriate strategy, used here, is to include all the relevant trials which meet the simple inclusion criteria.

BENEFITS AND DISBENEFITS

We have shown that cholesterol lowering interventions result in benefits for patients at high risk of coronary heart disease and disbenefits for subjects at lower risk. This extends the findings of previous overviews that have reported clearer benefits for cholesterol reduction in secondary prevention studies than in primary prevention trials.[11 13 17] However, because these overviews used the highly heterogeneous subgroups of studies of primary and secondary trials, they were not able to provide the distinct evidence of the benefit being dependent on risk shown here. Although a history of myocardial infarction or electrocardiographic evidence of coronary artery disease is a particularly good indicator of high risk of death from coronary heart disease, many other factors—for example, smoking, hypertension, diabetes, and peripheral vascular disease—are also associated with a greatly increased risk. The meta-analysis presented here shows the utility of moving beyond the simple dichotomy of primary and secondary prevention trials

Separating the trials into those testing pharmacological interventions and those using non-drug methods of lowering cholesterol reveals that mortality from non-coronary causes was increased in the former but not the latter. This observation, previously made in the course of an analysis of primary prevention trials,[7] complements the findings of epidemiological studies that there is no good evidence that naturally having a low blood cholesterol level in itself increases the risk of dying from causes other than coronary heart disease.[4 30 31] Furthermore, in the meta-analysis the degree of cholesterol lowering was not associated with the risk of mortality from non-coronary causes. Increased mortality from non-coronary causes therefore seems to be a property of cholesterol lowering drugs rather than cholesterol lowering itself. This adverse influence needs to be considered both when weighing up the costs and benefits of using the drugs in clinical practice and when planning the introduction of novel cholesterol lowering agents.

IMPLICATIONS OF RESULTS

The findings of the meta-analysis have implications for future trials of cholesterol lowering drugs. To be able to detect differences in total mortality as being statistically significant, larger trials have been advocated.[15] If these trials recruit subjects at very high risk, in order to achieve sufficient power, the results may be specific to this risk group and not generalisable to lower risk groups. Trials should perhaps be focused more at assessing the level of risk below which there is no net benefit, rather than confirming the results shown here of a positive net benefit in very high risk groups.

Trials which are currently running, or are likely to be established in the future, use statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), which reduce cholesterol more than the drugs used in most of the studies included in this meta-analysis. It may be anticipated, therefore, that the statins will result in greater reductions in mortality due to coronary heart disease, leading to a more favourable benefit:risk ratio than is seen with older drugs. The more powerful influence on serum cholesterol concentration of statins, however, is accompanied by other effects, such as a reduction in ubiquinone which could result in decreased cardiac performance.[32 33] In the only randomised trial of a statin with long follow up, the expanded clinical evaluation of lovastatin study,[30a-30c] 33 out of 6582 (0·50%) patients taking lovastatin were dead after one year, compared with only three out of 1663 (0·18%) patients taking the placebo ($\chi^2=3·15$; df=1; p=0·08), mostly (86%) from cardiac disease.[34] There is, therefore, no evidence which allows reassurance that statins will actually be associated with a higher benefit:risk ratio than older drugs, so current treatment decisions should remain based on the data included in the meta-analysis presented here until the results of ongoing trials become available.

Rose has remarked that "the purpose of risk assessment is not to categorise individuals according to a test result but rather to identify those who can be helped or helped most by preventive action."[35] McIsaac and colleagues,[36] examining the United States National Cholesterol Education Program guidelines,[37] have documented the considerable internal inconsistencies that can arise when guidelines fail to be risk based. Using estimates of risk of coronary heart disease from the Framingham study, they showed that drug therapy would be recommended for some groups of patients who are actually at much lower risk of coronary heart disease than other groups of patients who were not even deemed to be in need of specific dietary treatment.

WHO TO TREAT

The results of the present analysis can provide a useful standard against which to consider the various sets of guidelines that have been issued regarding the appropriate selection of people for consideration for pharmacological cholesterol lowering.[37-40] In the light of the findings reported here, it is of concern that current treatment guidelines, while generally mentioning the evaluation of overall coronary heart disease risk, do not map closely to actual risk of death from coronary heart disease and therefore to likely benefit. For example, the National Cholesterol Education Program guidelines suggest that drug therapy should be used if there is inadequate response to diet therapy and the individual has a low density lipoprotein concentration above 4·1 mmol/l (corresponding roughly to a total cholesterol concentration over 6·2 mmol/l) together with existing coronary heart disease or two other coronary heart disease risk factors.[37] However, since male sex and smoking are classified as "other coronary heart disease risk factors," a sizeable proportion of the population would fall into this category. In Scotland, for example, more than a quarter of men aged 40-59 could become candidates for drug treatment under these guidelines.[41]

Actual risks of death from coronary heart disease for such groups can be ascertained only from prospective epidemiological studies. In a region of the west of Scotland with high mortality due to coronary heart disease,[42] 45-64 year old male smokers with cholesterol concentrations over 6·5 mmol/l experienced a mortality risk of 12/1000 person years over a 12 year follow up period (C Hart, personal communication). Even taking into account underestimation of coronary heart disease risk because of the use of single cholesterol measurements—as opposed to the repeat measurements that should be taken in clinical practice—this group lies well below the risk level of 30/1000 person years, above which our meta-analysis of clinical trials suggests

benefit is seen. The new British Hyperlipidaemia Association guidelines on the detection and management of hyperlipidaemia[40] also seem to consider such a group to be at high priority for treatment with lipid lowering drugs in "diet resistant" cases (which most are likely to be[43]). Asymptomatic men with cholesterol concentrations over 7·8 mmol/l are also considered a priority for drug treatment, yet in the high risk west of Scotland population the coronary heart disease mortality for 45-64 year old men with cholesterol levels above this, at 13/1000 person years, is well below the risk level at which treatment seems to be beneficial. For women in this category the coronary heart disease mortality is about half of that of men.

The suggestion, based on the guidelines discussed above, that a quarter of middle aged men should be considered for treatment with cholesterol lowering drugs, clearly grossly overestimates the proportion of the population who would benefit from such treatment. In the Whitehall study[4] use of information regarding smoking status, presence of hypercholesterolaemia, hypertension, diabetes, angina, past heart attack, intermittent claudication, and obesity allows identification of 0·7% of 50-59 year old men with a risk of dying from coronary heart disease above 30/1000 person years, over an 18 year follow up period. For 40-49 year olds, as may be expected, the proportion of men at such a level of risk is even lower, at 0·1% (M Shipley, personal communication). These considerations confirm the view[35] that a strategy for prevention of coronary heart disease targeting lipid lowering drugs at individuals is likely to benefit only a small minority of the population and make only a minor contribution to control of the disease.

FAVOURABLE RISK-BENEFIT RATIO

The authors of the British Hyperlipidaemia Association guidelines correctly state that "lipid-lowering drug therapy should not be undertaken lightly as therapy is usually lifelong and its risk-benefit ratio should be carefully considered. The important clinical question is does the anticipated benefit of drug therapy in terms of reduction of coronary heart disease risk outweigh the imposition of long term drug therapy with the potential for unpredicted adverse effects."[40] The priorities given for lipid lowering treatment are, unfortunately, less fastidious than this statement implies. Similarly, the obvious but reasonable editorial opinion that cholesterol lowering drugs should be used "only if on our current knowledge the risk-benefit ratio for the individual is favourable"[44] is vitiated by a serious misunderstanding of the degree of coronary heart disease risk that is required before benefit is actually seen.[45] Despite the fact that the various guidelines and academic review articles indicate use of drug therapy for groups of patients for whom benefit has not been shown, they do at least point to the need for a degree of caution which is absent from either pharmaceutical company advertisements or their disguised promotional activities,[46,47] which potentially influence prescribing practice.[48]

There are several implications of our analysis for clinical practice and public health policy. Firstly, population screening for isolated raised cholesterol concentrations, whether in the high street or the general practitioner's surgery, is not curretly indicated. Such screening may, indeed, result in large numbers of people being treated for whom there are no benefits, or even net adverse effects. Secondly, cholesterol levels should not remain the principal focus of clinical guidelines aimed at preventing coronary heart disease. Instead, for the individual patient, global risk of coronary heart disease should be the variable of interest, and only those at very high risk of dying of coronary heart disease should be considered for treatment with currently available cholesterol lowering drugs. Thirdly, given that this analysis limits the appropriate domain of cholesterol lowering drug therapy to a relatively small group of patients at very high risk of coronary heart disease, the decision whether to prescribe cholesterol lowering drugs must be made in the context of the availability of a range of equally, or more, cost effective treatments.[25] Fourthly, randomised controlled trials large enough to reliably establish the effects of treatment on total mortality should focus on identifying the level of risk of coronary heart disease above which treatment is beneficial.

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Correction

Rationale for stopping cervical screening in women over 50

An editorial error occurred in this paper by W J Van Wijngaarden and I D Duncan (10 April, pp 967-71). The two figures on p 970 were transposed: the graph above the legend for figure 2 is actually figure 3, and vice versa; the legends are in the correct place.

Modified paediatric resuscitation chart

Two editorial errors and one authors' error occurred in this paper by Derek P Burke and David F Bowden (24 April, pp 1096-8). In the table of results the mean time for the calculation of correct volumes with Oakley's chart should have been 36·0 seconds, not 36·1. In the standard reference chart the concentration of adrenaline was incorrectly given as 1/1000 instead of 1/10 000. In the abstract and in the results the p value for the difference between the accuracy of calculations should have been $p < 0{\cdot}01$, not $p < 0{\cdot}05$. These errors do not affect the study's results.